UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/980,771	01/10/2002	Christophe D'Hulst	410.020	7483

20311 7590 08/06/2004

MUSERLIAN AND LUCAS AND MERCANTI, LLP
475 PARK AVENUE SOUTH
NEW YORK, NY 10016

EXAMINER	
RAO, MANJUNATH N	
ART UNIT	**PAPER NUMBER**
1652	

DATE MAILED: 08/06/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/980,771	D'HULST ET AL.	
	Examiner	Art Unit	
	Manjunath N. Rao, Ph.D.	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 February 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *20-28* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *20-28* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 20-28 are currently pending and are present for examination.

Applicants' amendments and arguments filed on 2-23-04, have been fully considered and are deemed to be persuasive to overcome the rejections previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. Specifically Examiner has withdraw all previous rejections as applied to claims 12-14 in view of claim cancellations. However, new rejections are in place as applied to the newly filed claims. Examiner has withdrawn the previous rejection of claims 12-14 under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Keeling et al. (WO 98/14601, 4-9-1998)mainly due to the fact that Keeling et al. do not teach or suggest the use of starch synthase isolated from *Chlamydomonas reinhardtii* for making the fusion protein.

Claim Objections

Claim 22 is objected to because of the following informalities: Claim 22 recites the word "sued" which appears to be a typographical error for the word "used". Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 20, 25 and claims 21-24, 26-28 depending therefrom are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and

distinctly claim the subject matter which applicant regards as the invention. Claims 20 and 25 recite the phrase " starch synthase GBSSI of *Chlamydomonas reinhardtii*, in the form of pre-protein of 708 amino acids...". It is not clear to the Examiner whether the pre-protein form of the enzyme is active as a starch synthase, if not what is the specific function/activity of said polypeptide.

Claims 20, 21, 25, 26 and claims 22-24, 27-28 which depend therefrom are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 20, 21, 25, 26 recite the phrase "corresponding to" in several instances. This use of this phrase does not definitely link the sequences with any other structural characteristics definitely. For example, in claim 20 the phrase "or a fragment of the GBSSI of *Chlamydomonas reinhardtii* represented by SEQ ID No: 3, in which the amino acid of the amino terminal end corresponds to that located in one of the positions 1 to 58 of SEQ ID No: 3..." or the phrase "the sequence SEQ ID No: 7 corresponding to a fragment of 438 amino acids of the peptide sequence of the GBSSI of *Chlamydomonas reinhardtii*," raises an ambiguity as to whether amino acids 1-58 of SEQ ID NO:3 is the N-terminal amino acids and whether the amino acids of SEQ ID NO:7 comprises is the fragment that is being referred to in the above phrases. This is because of the usage of "corresponding to " or corresponds to". Examiner suggests applicant to simplify the claim by using the term "comprises" which makes the phrase more definitive without any ambiguity.

Claims 20, 25 and claims 21-24, 26-28 depending therefrom are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 20 and 25 recite the phrase "or a fragment of the GBSSI of *Chlamydomonas reinhardtii* represented by SEQ ID No: 3" and "or a fragment thereof". Two things are not clear with respect to the above phrases. First whether this fragment continues to have the starch synthase activity or any type of function that can be measured and second, whether applicant considers the entire SEQ ID NO:3 as a fragment or a portion of the SEQ ID NO:3 as the fragment.

Claims 22, 27 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 22 and 27 recite the phrase "wherein the peptide or polypeptide is selected from ...". It is not clear to the Examiner as to which peptide or polypeptide that the applicant is referring to. From the context of the claim it appears that applicant is referring to the "peptide or polypeptide of interest". Correction is required.

Claims 22, 25 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 22 and 25 recite the following phrase,

"wherein the peptide or polypeptide of interest is selected from:

- those *encoding* biologically active peptides, especially peptides of therapeutic.." and
- "those *encoding* enzymes that are able to.."

It is well known in the art that it is the polynucleotides that encode polypeptides. However, polypeptides do not encode themselves. Correction is required.

Claims 22, 25 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 22 and 25 recite the phrase, "especially peptides of therapeutic interest" and "especially heat resistant". The metes and bounds of the phrase is not clear to the Examiner. Specifically, the scope of the word "especially" is not clear to the Examiner. Examiner suggests deletion of the above term.

Claim 23 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 23 recites the phrase "contains a cleavage site". Here again it is not clear to the Examiner as to what applicant means by the term "contains". Examiner suggests replacing the term with "comprises" or "comprising".

Claim 24 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 24 recites the phrase "several tens of μm". The metes and bounds of the phrase is not clear to the Examiner. Specifically it is not clear to the Examiner as to the range intended by the applicants with respect to the word "several", rendering the claim indefinite.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 20 –28 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a pharmaceutical composition comprising or consisting of a starch granule comprising a fusion protein wherein the fusion protein comprises or consists of a starch synthase comprising SEQ ID NO:3 or 5 encoded by SEQ ID NO:2 or 4 or comprising amino acid SEQ ID NO:7 or 9 encoded by 2 or 4 fused to a heterologous protein of interest with a therapeutic effect to its C-terminal encoded by a chimeric polynucleotide sequence, does not reasonably provide enablement for compositions comprising a fusion protein wherein the fusion protein comprises a fragment of either of the above polypeptide derived. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized in In re Wands (858 F.2d 731, 8 USPQ 2nd 1400 (Fed. Cir. 1988)) as follows: (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claim(s).

Claims 20-28 are so broad as to encompass a fusion protein comprising a fragment of starch synthase. The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of fragment polypeptides broadly

encompassed by the claims. Since the amino acid sequence of a protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired activity, requires a knowledge of and guidance with regard to which specific amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the proteins' structure relates to its function. However, in this case the disclosure is limited to the nucleotide and encoded amino acid sequence of only two fusion polypeptides comprising SEQ ID NO:3 or 7. It would require undue experimentation of the skilled artisan to make and use the claimed polypeptides. The specification is limited to teaching the use of fusion polypeptides comprising either SEQ ID NO:3 or 7 but provides no guidance with regard to those comprising fragments with unknown function. In view of the great breadth of the claim, amount of experimentation required to make the claimed polypeptides, the lack of guidance, working examples, and unpredictability of the art in predicting function from a polypeptide primary structure (e.g., see Ngo et al. in The Protein Folding Problem and Tertiary Structure Prediction, 1994, Merz et al. (ed.), Birkhauser, Boston, MA, pp. 433 and 492-495, Ref: U, Form-892), the claimed invention would require undue experimentation. As such, the specification fails to teach one of ordinary skill how to use the full scope of the polypeptides encompassed by this claim.

While recombinant and mutagenesis techniques are known and it is routine in the art to screen for multiple substitutions or multiple modifications, as encompassed by the instant claims, the positions within a protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining the desired activity/utility are limited in any

protein and the result of such modifications is unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g. multiple substitutions.

The specification does not support the broad scope of the claims which encompasses fusion proteins comprising all modifications and fragments of SEQ ID NO:3 or 7 because the specification does not establish: (A) regions of the protein structure which may be modified without affecting activity; (B) the general tolerance of starch synthases to modification and extent of such tolerance; (C) a rational and predictable scheme for modifying any amino acid residue with an expectation of obtaining the desired biological function; and (D) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including fusion proteins comprising enormous number of amino acid modifications of starch synthases. The scope of the claims must bear a reasonable correlation with the scope of enablement (*In re Fisher*, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of starch synthases having the desired biological characteristics for making fusion polypeptides is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See *In re Wands* 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

In response to the previous Office action, applicant has traversed the above rejection arguing that,

"the specification is enabling for the claims of the present scope which are directed to pharmaceutical compositions containing starch granules comprising fusion polypeptides between a polypeptide of interest and the granule bound starch synthase GBSSI of *Chlamydomonas reinhardtii* or fragments thereof which is clearly supported by the application and to pharmaceutical compositions containing said fusion polypeptides."

However, as explained above unless applicants provide a specific function for the fragment and the pre-protein, Examiner maintains that above claims are not enabled because those skilled in the art would not know as to which fragment has the same function as that of mature SEQ ID NO:3 or 7 and therefore would be reduced to the necessity of making and testing a large number of fragments which would lead to undue experimentation.

Claims 20-28 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 20-28 are directed to fusion polypeptides comprising fragments of SEQ ID NO:3 or 7. Claims 20-28 are rejected under this section of 35 USC 112 because the claims are directed to a genus of fusion polypeptides that have not been disclosed in the specification. No description has been provided of the fragment polypeptide sequences encompassed by the claim. No information, beyond the characterization of two fusion polypeptides comprising entire lengths of either SEQ ID NO:3 or 7 has been provided by applicants which would indicate that they had possession of the claimed genus of modified polypeptides. The specification does not contain any disclosure of the structure or function of all the fusion polypeptide sequences comprising fragments of SEQ ID NO:3 or 7, within the scope of the claimed genus. The genus

of polypeptides claimed is a large variable genus including peptides which can have a wide variety of structures. Therefore many structurally and functionally unrelated polypeptides are encompassed within the scope of these claims. The specification discloses only a single species of the claimed genus which is insufficient to put one of skill in the art in possession of the attributes and features of all species within the claimed genus. Therefore, one skilled in the art cannot reasonably conclude that applicant had possession of the claimed invention at the time the instant application was filed.

Applicant is referred to the revised guidelines concerning compliance with the written description requirement of U.S.C. 112, first paragraph, published in the Official Gazette and also available at www.uspto.gov.

Conclusion

None of the claims are allowable.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event,

however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Manjunath N. Rao, Ph.D. whose telephone number is 571-272-0939. The Examiner can normally be reached on 7.00 a.m. to 3.30 p.m. If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, Ponnathapura Achutamurthy can be reached on 571-272-0928. The fax phone numbers for the organization where this application or proceeding is assigned is 703-872-9306 for regular communications and for After Final communications. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 571-272-1600.

Manjunath N. Rao, Ph.D.
Primary Examiner
Art Unit 1652

July 29, 2004